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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/321,987	05/28/99	KIMBLE J	960296.95386

HZ12/1213

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EXAMINER
SHUKLA,R

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/321,987	KIMBLE ET AL.	
	Examiner	Art Unit	
	Ram R Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *14-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 & 5* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of the invention of group I, claims 1-13 in Paper No. 9 (filed 10-18-00) is acknowledged. The traversal is on the ground(s) that the similarities in the claims would require similar search. This is not found persuasive because as noted in the previous office action methods of the groups I and II can be practiced with different compositions and would identify compositions that are unrelated and would function by different mechanisms. Applicants argument that the step of identifying a nucleic acid affected by the treating step can be a way of observing a change in migration attributable to the presence of modulator is not persuasive because the nucleic acid obtained by the assay of group II may not be same as the target in the invention of group I because it could be any nucleic acid that plays a role in the migration of a developing gonadal cell and may not be a target of the compounds of group I.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-27 are pending in the instant application.

3. Claims 14-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

4. Claims 1-13 are instantly under consideration.

5.

Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2) (see claims 52 and 55 and the specification on pages 19 and 64). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 .

The specification on page 9, line 3 and figure 1C disclose amino acid sequences, however, these seqeences have not been listed in the sequence listing.

Applicants are required to submit a new sequence listing and CRF as noted in the Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures

Information Disclosure Statement

7. The first document (in the other documents category) in the information disclosure statement filed 9-7-99 has not been considered because it is a list of abstracts with titles only and it can not be determined what is the content of these abstracts.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 6-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the revised interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64, Number 244, page 71427-71440 (also available at www.uspto.gov).

When the claims are analyzed in light of the specification, instant invention encompasses methods comprising a target protein (I) that comprises a metalloprotease domain and a thrombospondin domain (ii) that is a homologue of any protein that comprises a metalloprotease domain and a thrombospondin domain, (iii) any protein that has 20% sequence similarity with said target protein, and (iii) any chimeric protein that comprises a metalloprotease domain and a thrombospondin domain. However, the specification discloses only gon-1, murine ADAMTS-1, bovine procollagen-1 N-proteinase, and human aggrecan-degrading metalloprotease. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, gon-1, murine ADAMTS-1, bovine procollagen-1 N-proteinase, and human aggrecan-degrading metalloprotease are the only species whose complete structure is either disclosed in the specification or is described in the art. The specification does not provide any disclosure as to what would have been the sequence of a homologue of any protein that comprises a metalloprotease domain and a thrombospondin domain, (iii) any protein that has 20% sequence similarity with said target protein, and (iii) any

chimeric protein that comprises a metalloprotease domain and a thrombospondin domain. It is noted that to practice the claimed method, an artisan has to know these embodiments since they are the target of the assay.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence). In the instant case, the only other identifying characteristic is the sequence identity of the claimed polynucleotides with a protein that comprises a metalloprotease domain and a thrombospondin domain. Since, the claimed invention encompasses protein sequences from any organisms, it is noted that the specification does not provide any disclosure whether these sequences from other species would have had same characteristics and functions or would have had additional characteristics or properties.

This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of sequence structure of the homologues of the proteins that comprises a metalloprotease domain and a thrombospondin domain, or that have 20% sequence similarity with said target protein, or any chimeric proteins that comprises a metalloprotease domain and a thrombospondin domain, gon-1, murine ADAMTS-1, bovine procollagen-1 N-proteinase, and human aggrecan-degrading metalloprotease, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

10. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the

breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

In the instant case the claimed method encompasses a method of identifying a modulator of a target protein (I) that comprises a metalloprotease domain and a thrombospondin domain (ii) that is a homologue of any protein that comprises a metalloprotease domain and a thrombospondin domain, (iii) any protein that has 20% sequence similarity with said target protein, and (iii) any chimeric protein that comprises a metalloprotease domain and a thrombospondin domain (iv) truncated form of said target protein using any target organism. However, the specification is not enabling for the claimed because the specification does not provide sufficient guidance, working example, and evidence as to whether an artisan of skill would have been able to make and use the claimed invention without undue experimentation.

First, the recited method is not enabling for the claimed method because the specification does not provide sufficient guidance as to how the method would be practiced. The specification in pages 20-27 discloses the cloning of gon-1 gene, its localization on chromosome and its expression profile in C.elegans using a GFP construct wherein putative gon-1 promoter drives the expression of gon-1. The specification also discloses the characterization of C.elegans mutants which have different alleles and parts of chromosomes using such mutants the specification teaches the characterization of gon-1 phenotype. However, the specificaiton does not provide any guidance or working example as to how the claimed assay will be carried out. As currently written, claims recite two steps in the method, treatment of an organism which has a gonadal cell responsive to the protein with a potential modulator and observing the change in migration or shape of the developing gonadal cell, however, it is not clear whether gon-1 is the only gene that is responsible for gonadal cell migration in all the organisms or even in C.elegans. If not, the change in the migration or shape of the gonadal cell may result due to the effect of the compound on any protein other than the recited proteins and there is nothing in the method to indicate that the method would only target gon-1 or a protein that comprises a metalloproteinase and thrombospondin. In other words, claimed method would not be able to indicate that a compound modulates the function of a

protein as recited, since it can not be excluded that the observed changes are not due to any other protein function modulation. Additionally, the method recites identifying a modulator of a protein, however, the change in the migration of the cell may not indicate a change in the protein, rather it would indicate the change in the function of the protein.

Regarding the practice of the invention in any and all organisms, it is not enabling for use in all the organisms, including in C.elegans because the specification does not teach how would the invention be practiced in any organism, for example, how would the compounds (listed in claim 13) would be administered to any organism such that it would reach the developing gonadal cell of said organism. While the specification teaches making of C.elegans mutants with different alleles and gon-1 gene, it does not provide any guidance as to how the claimed method would be carried out in C.elegans. The specification on page 12 dislcoses that a putative modulator can be added to the growth medium or injected into the organism or introduced by transformation and the effect can be determined by monitoring the change in the migration of cell or by selection for sterility and the specification provides references for convention methods (see lines 27). However, it is not clear how can migration of cell or sterility can indicate that the change is due to only a certain protein function not any other function. Furthermore, the specification does not provide any guidance as to how the method would be practiced in any other organisms, for example, in a mouse or in a bird or a human etc or any other nematode. It is noted that the phylum nematoda itself contains about 12,000 species which have different size, are parasitic to animals or plants (see Villee et al. General Zoology, Chapter 24, pages 509-514, 1984, Saunders College Publishing, NY) and there is nothing in the specification to indicate that the proteins recited in the claims would have had affect gonadal cell migration in any and all nematodes. If there is not evidence that the recited proteins affect gonadal cell migration in all the nematodes, it is not clear how can these proteins alter gonadal cell migration in other organisms. The limited amount of porphetic guidance for carrying out the invention in C.elegans is not sufficient to support the enablement of the claimed invention in any organisms and an artisan would have required undue experimentation to figure out the criteria for monitoring the effects of a compound on a protein.

Next, would any and all proteins that comprise a metalloprotease and a thrombospondin motif have a role in gonad development or gonadal cell migration in any and all organisms or

even in a nematode. For example, the invention lists a murine protein ADAMTS-1, a bovine protein and a human protein which comprise a metalloprotease and a thrombospondin motif. However, there is no evidence in the specification or in the art to show that these proteins have any role in gonadogenesis or gonad development or gonadal cell migration. For example, Kuno et al describe ADAMTS-1 as a gene highly expressed in vivo in colon 26 cachexigenic tumor (Kuno K et al. The J of Biological Chemistry 274:18821-18826, 1999). While it has been shown that ADAMTS-1, a member of ADAMs family of proteins, is incorporated in ECM, there is not evidence that this protein has a role in gonadal cell migration. Furthermore, the metalloprotease motif of ADAMTS-1 is inactive due to the lack of Zinc-binding motif (see the introduction section in columns 1 and 2 on page 18821) therefore, it is not clear whether ADAMTS-1 will have the characteristic metalloprotease activity of this class of molecules or even be functional in C.elegans or would have gon-1 function. Likewise, there is no evidence whether other two metalloproteases would also have the gon-1 like activity and therefore, it is not clear whether one can call these recited metalloproteases true homologues of gon-1 when only known similarity is in the sequence but no functional similarity is known. It is further noted that the Colige et al (Colige A et al. Proc. Natl. Acad. Sci. USA 94:2374-2379, 1997) reported the cloning and characterization of the bovine procollagen-I N-ptroteinase. However, they did not describe whether this protein was expressed in gonads (see figure 6 in Colige et al). Again, there is no evidence whether bovine collagenase-I N-protease has any role in gonadal cell migration. In summary, there is no evidence in the specification or in the art to suggest any of the proteins recited in claim 9 has a role in gonadal cell migration. Next, the specification is also not enabling for the target proteins being a fragment or truncated forms of gon-1 or any other recited proteins because there is not evidence whether these embodiments would have any biological activity or whether they would affect gonadal cell migration. It is noted that Inventors own work indicates that gon-1 is functional only when it has both the metalloprotease and the thrombospondin domains (see last two paragraphs in column 1 on page 588 of Belloch R and Kimble J . Nature 399:586-590, 1999). The specification does not teach which parts of proteins comprising metalloprotease and thrombospondin motifs can be removed without affecting its activity in gonadal cell migration.

Next, regarding the practice of the methods wherein the target protein has 20% sequence similarity to gon-1 or its recited homologues, the issue is: would all these proteins

have the biological activity required for gonadal cell migration because as claimed the proteins would have up to 80% amino acid sequence different than the wild type proteins, however, there is no evidence whether a protein with such a low sequence similarity will have the functional activity at the wild type protein, particularly when the inventor themselves have shown that both the metalloproteinase and the thrombospondin domains are required for activity. For example gon-1 gene encodes a protein of 2150 amino acids and changing 80% amino acids of this protein would mean that 1750 amino acids of GON-1 can be altered by deletion, substitution, and addition. It is recognized in the prior art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence, and the functional properties of the different parts of the protein (see second paragraph in Rudinger J in Peptide Hormones. Editor Parsons JA. Pages 1-7, 1976, University Park Press, Baltimore). Rudinger further add, "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study" (see conclusion on page 6). The specification does not teach which changes in the amino acid sequence or which 80% amino acids of GON-1 or any other protein with metalloproteinase and thrombospondin can be changed such that the resultant protein would still retain the function of GON-1 or corresponding wild type protein. The specification does not teach how to use the method in an organism that has a mutant protein acid that is derived from the recited wild type protein but did not have the function of the starting protein. As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In summary, the specification is not enabling for the claimed invention because the specification as filed does not provide sufficient guidance, working example and evidence as to

how as to how an artisan would practiced the claimed invention without required undue experimentation.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the at least one modulator" in line 9. There is insufficient antecedent basis for this limitation in the claim since first step of the method recites "at least one potential modulator".

Claims 6-8 are vague and indefinite because it is unclear as to what is meant by the limitation "polynucleotide coding sequence".

Claims 6 is also vague and indefinite because it is unclear as to what is meant by the limitation "a chimeric protein encoded at least in part by at least one of the foregoing", since the embodiments recited earlier in the claim are proteins.

Claim 6 is also vague and indefinite because it is unclear as to what would be considered "sufficiently close." Since the term "sufficiently" is a relative term, the metes and bounds of the invention are not clear.

Claim 13 is unclear because it recites the phrase "at least one modulator " rather than the "at least one potential modulator". How can one know a whether a compound is a modulator before carrying out the assay?

13. Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: wherein a change in the migration or shape of the developing gonadal cell results in the identification of the modulator.

14. No claim is allowed.

15. Following articles by the inventors are made of record:

a. International Publication Number WO 99/61656, dated 12-2-1999.

b. Blelloch R et al. Dev. Biol. 216:382-93, 1999.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Ram R. Shukla, Ph.D.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Application No.: 09/321,987

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Specification contains amino acid sequences which are not included in the Seq. Listing.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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